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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/539,756 | 04/14/2006 | Kenji Sasaki | P28062 | 5026 |

7055 7590 06/12/2009

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| EXAMINER | |
|---|---|
| GUSSOW, ANNE | |
| ART UNIT | PAPER NUMBER |
| 1643 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 06/12/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/539,756 | SASAKI ET AL. | |
| | Examiner | Art Unit | |
| | ANNE M. GUSSOW | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17 and 19-21* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1, 16, and 17 have been amended.

Claim 18 has been cancelled.

2. Claims 2-4 and 19-21 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 14, 2008.

3. Claims 1 and 5-17 are under examination.

4. The following office action contains NEW GROUNDS of Rejection.

### *Rejections Withdrawn*

5. The rejection of claims 1, 5, and 6 under 35 U.S.C. 112 2nd paragraph as being indefinite is withdrawn in view of applicant's amendment to claim 1.

6. The rejection of claims 1 and 7-18 under 35 U.S.C. 102(a) as being anticipated by Kouno, et al. is withdrawn in view of applicant's translation of the foreign priority document.

7. The rejection of claims 1 and 5-17 under 35 U.S.C. 103(a) as being obvious over Kouno, et al. in view of Thompson is withdrawn in view of applicant's translation of the foreign priority document.

8. The rejection of claims 1 and 7-18 on the grounds of non-statutory obviousness type double patenting as being unpatentable over claims 1, 3, 10, 12, 14, 16, and 17 of copending Application No. 10/497,516 is withdrawn in view of applicant's terminal disclaimer filed March 24, 2009 and approved on June 6, 2009.

***Rejections Maintained/NEW GROUNDS of Rejection***

***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. The rejection of claims 7-17 under 35 U.S.C. 112, 2nd paragraph as being indefinite for reciting the phrase "adding a compound which has a disulfide bond in the molecule" in claim 7 is maintained. It is not clear if the molecule is the same as the compound or if it is a different molecule. For the purposes of this office action the molecule and compound are interpreted as being the same compound. Applicant's response has amended claim 1 (and thus obviated the rejection of claim 1) however, applicant has not amended the same language in claim 7.

11. The rejection of claims 16 and 17 under 35 U.S.C. 112, 2nd paragraph as being indefinite for reciting the phrase "represented by" is maintained. Applicant's response has partially amended claims 16 and 17 however; the claims still recite that the monoclonal antibody comprises sequences "represented by" SEQ ID Nos. 1, 2, and 3 in claim 16 and SEQ ID No. 8 in claim 17. Amending claims 16 and 17 to recite "of SEQ

ID Nos. 1, 2, and 3" in claim 16 and "of SEQ ID No. 8" in claim 17 would overcome this rejection.

12. Claims 5 and 6 recite the limitation "in the molecule" in line 2 of the claims. There is insufficient antecedent basis for this limitation in the claim.

13. Claims 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite for reciting the phrase "adding a compound which has a disulfide bond in the molecule" in claim 7. In view of the dependent claims, the compound being added is cysteine, homocysteine, or dihydrolipoic acid which each contains thiol groups but not a disulfide bond. Thus, for the purposes of this office action claim 7 is being interpreted to mean "adding a compound which has a thiol group in the molecule" in view of the dependent claims.

### *Claim Rejections - 35 USC § 102*

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Hosokawa, et al. (US PAT 5,767,246, issued June 16, 1998, as cited on the IDS filed October 21, 2005).

The claims recite a method for protecting a thiol group in a protein having a free cysteine residue, which comprises adding a compound which has a disulfide bond in the molecule and exerts no influence on the activity of the protein simultaneously or separately from a compound which has a thiol group in the molecule and exerts no influence on the activity of the protein, wherein the compound which has a thiol group in the molecule and exerts no influence on the activity of the protein is cysteine, homocysteine, glutathione or dihydrolipoic acid.

Hosokawa, et al. teach production of a thiolated antibody by adding L-cysteine and polyethylene glycol (PEG) to an antibody in solution (example 7, column 14). Hosokawa, et al. teach that the thiolated antibody possesses a strong anti-cancer effect (experiment 6, column 16) thus the addition of the L-cysteine had no effect on the activity of the compound. In view of the 112 2nd paragraph indefiniteness rejection, above, the claims are being interpreted to mean "addition of a compound comprising a thiol group" and the thiol-PEG which is added to the antibody comprises a thiol group. Since the claims require the addition of the compound to have no influence on the activity of the protein and Hosokawa, et al. add L-cysteine to an antibody which has no effect on the binding activity of the antibody (see Figure 5), all the limitations of the claims have been met.

***Claim Rejections - 35 USC § 103***

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1 and 5-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hosokawa, et al. (US PAT 5767246 issued June 16, 1998, as cited on the IDS filed October 21, 2005) in view of Glassy, et al. (Biotechnology and Bioengineering, 1988. Vol. 32, pages 1015-1028) and further in view of Sykes, et al. (US PAT 6,313,274, issued November 6, 2001).

Claims 7-9 have been described supra. Claims 1, 5, 6, and 10-17 recite a method for protecting a thiol group in a protein having a free cysteine residue and wherein the protein is produced by using a cell cultured in a serum-free medium, comprising adding a compound which has a disulfide bond and exerts no influence on the activity of the protein, wherein the compound which has a disulfide bond in the molecule and exerts no influence on the activity of the protein is cystine, homocystine, lipoic acid or oxidized glutathione, wherein the protein is a recombinant protein, wherein the protein is an antibody, wherein the antibody is an F(ab')2 antibody, wherein the antibody is a monoclonal antibody, wherein the monoclonal antibody has a thiol group in its variable region, wherein the monoclonal antibody has a free cysteine residue in its variable region, wherein the monoclonal antibody comprises the amino acid sequences represented by SEQ ID NOs: 1, 2 and 3 in the Sequence Listing in its heavy chain hypervariable region, and the amino acid sequences of SEQ ID NOs:4, 5 and 6 in the Sequence Listing in its light chain hypervariable region, wherein the monoclonal antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:7 in the Sequence Listing and a light chain variable region containing the amino acid sequence represented by SEQ ID NO:8 in the Sequence Listing.

Hosokawa, et al. has been described supra. Hosokawa, et al. also teach the thiolated protein is an F(ab')2 antibody GAH. The GAH antibody has the same sequence as the instant antibody CDRs SEQ ID Nos. 1-6 and variable regions SEQ ID Nos. 7 and 8 (see sequence alignments in the office action appendix mailed March 27, 2008). Hosokawa, et al. do not teach culturing the antibody in serum free media or addition of cystine. These deficiencies are made up for in the teachings of Glassy, et al. and Sykes, et al.

Glassy, et al. teach production of antibodies by culturing hybridomas in serum free media which exhibit increased antibody secretion compared to hybridoma cultured in serum-supplemented medium and the hybridomas have comparable growth behavior when cultured either with or without serum (see entire document, particularly page 1020 2nd column and page 1022 2nd column).

Sykes, et al. teach that the terms cysteine, cystine, and half-cystine are often used interchangeably with the correct meaning being apparent from the context (column 6 lines 58-63).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the thiolated antibody of Hosokawa, et al. in a serum free media as taught by Glassy, et al. with the cystine in view of Sykes, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced the thiolated antibody of Hosokawa, et al. in a serum free media as taught by Glassy, et al. with the cystine in

view of Sykes, et al. because Hosokawa, et al. teach production of a thiolated antibody by adding L-cysteine and polyethylene glycol (PEG) to an antibody in solution and the thiolated antibody possesses a strong anti-cancer effect and Glassy et al. teach that culturing hybridomas in serum free media increases antibody secretion compared to hybridomas cultured in serum-supplemented medium and the antibodies have comparable growth behavior when cultured either with or without serum. As set forth above, in view of the 112 2nd paragraph indefiniteness rejection, above, the claims are being interpreted to mean "addition of a compound comprising a thiol group" and the thiol-PEG which is added to the antibody comprises a thiol group. Additionally, Sykes, et al. teach that the terms cysteine and cystine are often used interchangeably, thus, one of ordinary skill in the art would use either cysteine or cystine for the addition of the thiol group. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have produced the thiolated GAH F(ab')2 antibody of Hosokawa et al., which necessarily comprises the variable regions of SEQ ID Nos: 7 and 8 (inclusive to the CDRs of SEQ ID Nos: 1-6) and necessarily comprises free thiol groups in the variable region in the cysteine residues of the variable region in serum free media in order to increase antibody secretion. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable

expectation of success in making the above modifications in view of Glassy, et al, providing evidence that hybridomas cultured with or without serum have comparable growth behavior. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the thiolated GAH F(ab')2 antibody of Hosokawa, et al. in a serum free medium in view of Glassy, et al. and Sykes, et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

***Conclusion***

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
June 7, 2009

/Anne M Gussow/
Examiner, Art Unit 1643